

REMARKS

Claims 1-16, and 18-74 are pending and under examination with claims 66-69 having been withdrawn from consideration as being directed to a non-elected invention. Applicants reserve the right to pursue these claims in a later filed application claiming the benefit of the subject application. By the present communication, claims 1 and 18 have been amended to define Applicants' invention with greater particularity. Support for the amendments can be found throughout the application as filed. In particular, support for the amendments can be found at, for example, paragraphs [0042]-[0043]. Accordingly, the amendments do not raise an issue of new matter. Applicants have reviewed the Office Action mailed February 26, 2007, and respectfully traverse all grounds of rejection for the reasons that follow.

Rejections under 35 U.S.C. §101

Applicants respectfully traverse the rejection of claims 1-16 and 18-33 under 35 U.S.C. §101 as allegedly being directed to non-statutory subject matter. Specifically, the Office maintains that claims 1-16 and 18-33 lack a final result that is a physical transformation and thereby do not produce a tangible result.

Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 1 to recite a computer readable medium or media having stored thereon computer-implemented instructions causing a processor to perform the steps of providing both a data structure relating a plurality of reactants to reactions of a biochemical network and a constraint set and determining at least one flux distribution wherein the flux distribution determines a systemic property that is dependent upon a regulated reaction, and providing information resulting from the foregoing steps to a user. In light of these amendments, Applicants respectfully submit that the claims produce a tangible result, and request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claim 18 under 35 U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action alleges that claim 18 recites the limitations “said commands” and “said data representation,” which lack antecedent basis, and the limitation “feasible flux distributions,” which is a relative term. Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 18 to cure any deficiencies with regard to antecedent basis, rendering these grounds for rejecting claim 18 moot. With regard to the assertion that the term “feasible” renders claim 18 indefinite, Applicants respectfully disagree.

The purpose of the definiteness requirement is to “ensure that the claims delineate the scope of the invention using language that adequately notifies the public of the patentee’s right to exclude.” *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347-48 (Fed. Cir. 2005) (internal citation omitted). Claims are considered indefinite when they are “not amenable to construction or are insolubly ambiguous Thus, the definiteness of claim terms depends on whether those terms can be given any reasonable meaning.” *Id.* Indefiniteness requires a determination whether those skilled in the art would understand what is claimed. To make that determination, we have explained that “in the face of an allegation of indefiniteness, general principles of claim construction apply.” *Id.* at 1348. In that regard, claim construction involves consideration of primarily the intrinsic evidence, viz., the claim language, the specification, and the prosecution history. *Phillips v. AWH Corp.*, 415 F.3d 1202, 1314 (Fed. Cir. 2005) (*en banc*).

The specification, at [0112], describes the phrase “feasible flux distributions” with clarity to the skilled reader:

To determine the metabolic capabilities of a defined metabolic genotype the above equation is solved for the metabolic fluxes and the internal metabolic reactions, v , while imposing constraints on the activity of these fluxes. Typically the number of metabolic fluxes (n) is greater than the number of mass balances or metabolites (m) (i.e., $n > m$) resulting in a **plurality of**

feasible flux distributions that satisfy this equation and any constraints placed on the fluxes of the system. This range of solutions is indicative of the flexibility in the flux distributions that can be achieved with a given set of metabolic reactions. The solutions to this equation lie in a restricted region. This subspace defines the capabilities of the metabolic genotype of a given organism, since the allowable solutions that satisfy this equation and any constraints placed on the fluxes of the system define all the metabolic flux distributions that can be achieved with a particular set of metabolic genes. (Paragraph [0112], emphasis added).

It is respectfully submitted that the above excerpt from the specification clearly sets forth the meaning of the term “feasible” in the phrase “feasible flux distributions” to refer to those flux distributions that satisfy the equation disclosed in paragraph [0111] for the metabolic fluxes and the internal metabolic reactions as well as any constraints put on the system. It is further submitted that the meaning of “feasible” in this context is in accord with the ordinary meaning of the term.

Applicants submit that, when viewed in light of the specification of which it is a part, claim 13 is sufficiently clear and definite to the skilled person, thereby complying with the second paragraph of section 112 of the Code. Accordingly, withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1-9, 11, 14-15, 18-28, 30, 32-33, 34-42, 44-45, 48-49, 51-60, 62-63 and 70-74 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, *et al.* (*AICHE Journal* 42(5): 1996-2005 (1996); hereinafter “Hatzimanikatis”). Specifically, the Office Action alleges that it would have been obvious for someone of skill in the art to automate the method of Hatzimanikatis to result in the instantly claimed method because automation of a manual activity is a rationale for obviousness.

To establish a *prima facie* case of obviousness, the Office must show that the prior art would have suggested the claimed invention to one of ordinary skill in the art and that it could have been carried out with a reasonable likelihood of success when viewed in the light of the prior art. *Brown & Williamson Tobacco v. Philip Morris*, 229 F.3d 1120, 1124 (Fed. Cir. 2000),

accord *In re Royka*, 180 USPQ 580 (C.C.P.A. 1974) (to establish *prima facie* obviousness, all claim limitations must be taught or suggested by the prior art); M.P.E.P. §2143.03. The recent U.S. Supreme Court decision in the *KSR International v. Teleflex Inc.* (82 USPQ2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

Contrary to the assertion by the Office Action, Hatzimanikatis does not teach or suggest providing a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction, as required by the instant claims. At most, Hatzimanikatis describes a mathematical framework for determining changes in regulatory structure and strength that should be considered to optimize a particular metabolic process (see page 1278, 2nd col., 3rd paragraph). Hatzimanikatis indicates that it deals with a mathematical description of a metabolic pathway with a postulated number of regulatory loops and that the objective is to determine which of the regulatory loops should be retained (page 1279, 1st col., 1st complete paragraph). Hatzimanikatis further describes consideration of a “regulatory superstructure” in which every metabolite in the system can potentially regulate any enzyme in that system (page 1279, 1st col., 3rd complete paragraph). The theoretical approach is followed in order to find the optimal regulatory structure for maximization of phenylalanine selectivity in the microbial aromatic amino acid synthesis pathway. From the eight feedback inhibitory loops in the original regulatory structure of this pathway, inactivation of at least three loops and overexpression of three enzymes increased phenylalanine selectivity. Hatzimanikatis concludes at page 1289, left column, final paragraph:

The problem of designing the regulatory structures built around a given metabolic reaction network was formulated as a MILP optimization problem. A synthesis approach has been proposed which assumes that the metabolic pathway of interest has no regulation, and considers which regulatory structure optimizes the objective.

However, Hatzimanikatis provides no teaching or suggestion of a computer readable medium or media having stored thereon computer-implemented instructions causing a processor to perform the steps that include providing a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction. Contrary to Hatzimanikatis, the claimed methods are not directed to finding a regulatory structure to optimize the objective, but rather at imposing information about regulation in determining optimal values of networks with one or more regulatory constraints defined. Accordingly, Applicants respectfully submit that the claimed methods are unobvious over Hatzimanikatis, and request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 10, 12, 43, and 46 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, as applied to claims 1-9, 14-15, 18-28, 30, 32, 33, 34-42, 44, 45, 48, 49, 51-60, 62-63 and 70-74, and further in view of Grewal, *et al.* (Protein Engineering 7:205-211(1994); hereinafter, "Grewal"). Specifically, the Office Action relies upon Grewal as allegedly describing a reaction pathway in a multicellular organism where the reaction in one cell mediates cellular interaction in the multicellular organism. The arguments presented above with regard to Hatzimanikatis apply equally and are incorporated here. Accordingly, Applicants respectfully submit that the deficiencies of Hatzimanikatis are not cured by viewing Hatzimanikatis in combination with Grewal, and request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 31, and 64-65 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, as applied to claims 1-9, 14-15, 18-28,

30, 32, 33, 34-42, 44, 45, 48, 49, 51-60, 62-63 and 70-74, and further in view of Liao, *et al.* (Biotechnology and Bioengineering 52:129-140 (1996); hereinafter, "Liao"). This rejection relies on Hatzimanikatis et al. as the primary reference. The arguments presented above with regard to Hatzimanikatis apply equally and are incorporated here. Thus, Applicants have set forth the deficiencies of Hatzimanikatis, which are not cured by viewing Hatzimanikatis et al. in combination with Liao et al. Accordingly, Applicants respectfully submit that the claimed methods are unobvious over Hatzimanikatis in view of Liao, and request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 16 and 50 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, as applied to claims 1-9, 14-15, 18-28, 30, 32, 33, 34-42, 44, 45, 48, 49, 51-60, 62-63 and 70-74, and further in view of Kim, *et al.* (U.S. 2002/00087275; hereinafter, "Kim"). This rejection relies on Hatzimanikatis et al. as the primary reference. The arguments presented above with regard to Hatzimanikatis apply equally and are incorporated here. Thus, Applicants have set forth the deficiencies of Hatzimanikatis, which are not cured by viewing Hatzimanikatis in combination with Kim. Accordingly, Applicants respectfully submit that the claimed methods are unobvious over Hatzimanikatis in view of Kim, and request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 13 and 47 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, as applied to claims 1-9, 14-15, 18-28, 30, 32, 33, 34-42, 44, 45, 48, 49, 51-60, 62-63 and 70-74, and further in view of Vissing, *et al.* (Neurology 47:766-771 (1996); hereinafter, "Vissing"). This rejection relies on Hatzimanikatis et al. as the primary reference. The arguments presented above with regard to Hatzimanikatis apply equally and are incorporated here. Thus, Applicants have set forth the deficiencies of Hatzimanikatis, which are not cured by viewing Hatzimanikatis in combination with Vissing. Accordingly, Applicants respectfully submit that the claimed methods are unobvious over Hatzimanikatis in view of Vissing, and request withdrawal of the rejection.

In re Application of:
Palsson et al.
Application Serial No.: 10/087,441
Filed: March 1, 2002
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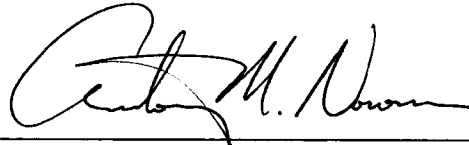
PATENT
Attorney Docket No.: UCSD1330-2

CONCLUSION

In summary, for the reasons set forth herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge \$60.00 as payment for the Petition for One-Month Extension of Time fee to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,



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